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(54) Title: ETHERS OF O-DESMETHYL VENLAFAXINE

(57) Abstract: This invention provides O-α-acyloxyalkyl ethers of the venlafaxine metabolite 4-[2-(Dimethylamino-1-(1-hydroxycyclohexyl)ethyl]phenol, represented by Formula (I); wherein the configuration at the steriogenic center (*) may be R, S, or RS (the racemate); R_1 is selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, or the moiety: (a); R_2 is selected from H, or C_1-C_6 alkyl; or, R_1 and R_2 may be concatenated such that (i), form a moiety having formula (b); R_3 is selected from H or C_1-C_6 alkyl; and R_4 and R_5 are independently selected from H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 thioalkoxy, -CN, -OH, -CF_3, -OCF_3, halogen, -NH_2, -NO_2, or mono or dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, or pharmaceutically acceptable salts or hydrates thereof, R, S, or RS forms thereof; as well as pharmaceutical compositions and methods treating central nervous system disorders.

ETHERS OF O-DESMETHYL VENLAFAXINE

This invention relates to ethers of O-desmethyl venlafaxine, more particularly to O-α-acyloxyalkyl ethers of 4-[2-(Dimethylamino-1-(1-hydroxycyclohexyl)ethyl]-phenol, processes for preparing them as well as pharmaceutical compositions and uses thereof.

Background of the Invention

Various patents and literature references describe the biological activities of venlafaxine, and its salts and analogs. Venlafaxine hydrochloride tablets are marketed by Wyeth-Ayerst Laboratories as EFFEXOR.

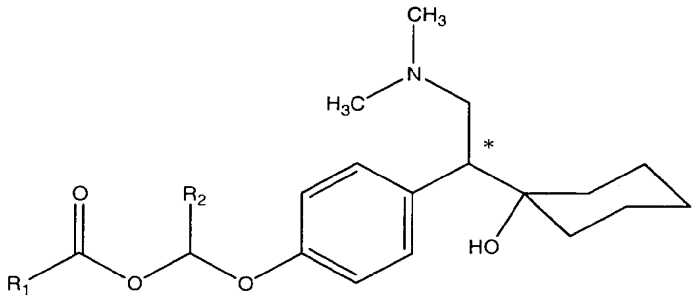
The absolute configuration of the (+) enantiomer of venlafaxine was established as S by a single crystal X-ray analysis of the hydrobromide salt and the anomalous dispersion technique (Yardley et al., J. Med. Chem., 1990, 33, 2899).

(R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol and its metabolites 1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol and 1-[1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol are disclosed and claimed in U.S. Patent No. 4,535,186 (Husbands et al.). U.S. Patent No. 5,530,013 (Husbands et al.) claims the use of venlafaxine in the inducement of cognition enhancement. U.S. Patent No. 5,506,270 (Upton et al.) claims venlafaxine's use in methods of treating hypothalamic amenorrhea in non-depressed women.

U.S. Patents Nos. 5,788,986 (Dodman) and 5,554,383 (Dodman) teaches and claims the use of serotonin reuptake inhibitors in modifying the behavior of dogs.

Detailed Description of the Invention

This invention provides pharmaceutically active O-α-acyloxyalkyl ethers of the venlafaxine metabolite 4-[2-(Dimethylamino-1-(1-hydroxycyclohexyl)ethyl] phenol ("O-Desmethyl venlafaxine" or "ODV") having the structural formula I

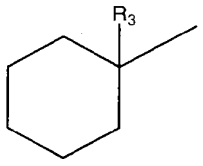


(I)

wherein

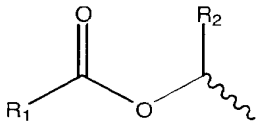
the configuration at the steriogenic center (*) may be R, S, or RS (the racemate);

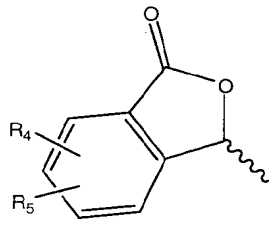
R_1 is selected from $C_1 - C_6$ alkyl, $C_1 - C_6$ alkoxy, $C_3 - C_6$ cycloalkyl, or the moiety:



(a);

R_2 is selected from H, or $C_1 - C_6$ alkyl; or,

R_1 and R_2 may be concatenated such that  , form a moiety having formula (b):



(b);

R_3 is selected from H or C_1 – C_6 alkyl; and

R_4 and R_5 are independently selected from H, C_1 – C_6 alkyl, C_3-C_6 cycloalkyl, C_1 – C_6 alkoxy, C_1 – C_6 thioalkoxy, -CN, -OH, -CF_3, -OCF_3, halogen, -NH_2, -NO_2, or –$N(CH_3)_2$, or pharmaceutically acceptable salts or hydrates thereof.

In some preferred embodiments of the present invention R_1 is t-butyl, methoxy, or isobenzofuranone.

In other preferred embodiments of the invention R_2 is C_1 – C_3 alkyl and in still more preferred embodiments of the invention R_2 is methyl.

Specific examples of compounds of Formula I include:

{4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy}methyl pivalate;

1-{4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy}ethyl propionate; and

3-{4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy}-2-benzofuran-1(3H)-one.

Particularly, this invention provides compounds and/or compositions of both the O-α-acyloxyalkyl R-ether of Formula I and the O-α-acyloxyalkyl S-ether of Formula I, both being substantially free of the other. In addition, the invention

provides the O-α-acyloxyalkyl RS-ether of 4-[2-(Dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]-phenol of Formula I.

Substantially free, as used herein means the compound or composition is made up of significantly greater proportion of the desired isomer than of the optical antipode. In a preferred embodiment of the invention, "substantially free" means that the compound or composition is made up of at least about 90% of the desired isomer and about 10% or less of the optical antipode. In still more preferred embodiments of the present invention, the compound or composition is made up of at least about 95% of the desired isomer and about 5% or less of the optical antipode. In yet further embodiments of the present invention the compound or composition is made up of at least about 99% of the desired isomer and about 1% or less of the optical antipode. Preferably the characterized or separated enantiomer will exhibit physical properties of a fully characterized compound, i.e. a uniform melting point and a uniform rotation of plane-polarized light in a polarimeter. Most preferably, the enantiomers will be recrystallized to analytical purity.

$C_1 - C_6$ alkyl as used herein, such as in the definition of R_1, includes straight or branched chain alkyl groups within the specified range of carbon atoms, eg methyl, ethyl, propyl, n-butyl or t-butyl.

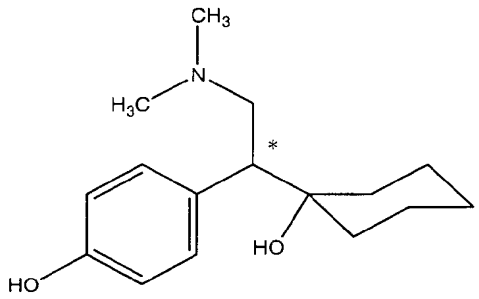
Halogen, as used herein refers to chlorine, bromine, iodine and fluorine.

Pharmaceutically acceptable salts refer to salts prepared from pharmaceutically acceptable acids, including inorganic acids and organic acids, such as, but not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, mitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic and the like.

Compounds of the invention are readily prepared by methods known in the art, for instance, as described by Bodor, et al., *J. Org. Chem.*(48) 5280-5284 (1983). Where necessary any reactive substituent group or atom may be protected prior to any reaction and deprotected afterwards.

Accordingly this invention provides a process for preparing a compound of formula (I) as defined herein, or a pharmaceutically acceptable salt or hydrate thereof, which process comprises one of the following:

(i) reacting R-, S-, or (R/S)- 4-[2-(dimethylamino-1-(1-hydroxycyclohexyl)ethyl]-phenol of formula:



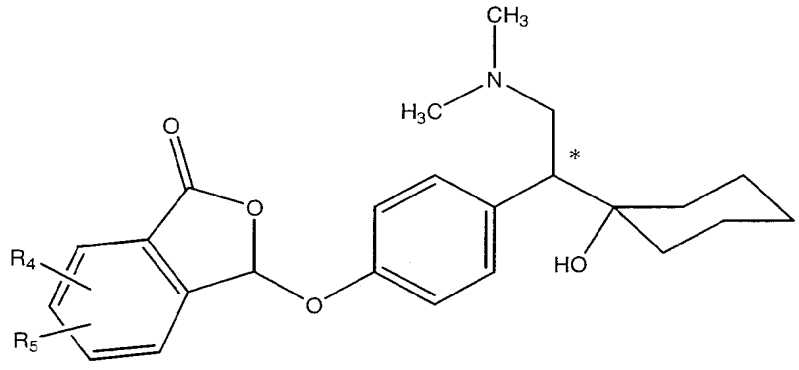
(II)

or a salt thereof, with a compound having the formula (V)

$$R_1 - CO - CHR_2 - X \qquad (V)$$

where R_1 and R_2 are as defined above subject to the proviso that a reactive substituent group, eg an -OH or $-NH_2$ substituent on the concatenated R_1 and R_2 group may be protected by a protecting group that is subsequently removed and X is a leaving group for example a halogen atom such as chlorine, bromine or preferably iodine; or

(ii) subjecting a compound having formula (IV)



(IV)

wherein:

the configuration at the stereogenic center (*) may be R, S, or RS (the racemate) and R_4 and R_5 are independently selected from H, $C_1 - C_6$ alkyl, $C_1 - C_6$ alkoxy, $C_1 - C_6$ thioalkoxy, -CN, -OH, $-CF_3$, $-OCF_3$, halogen, $-NH_2$, $-NO_2$, or $-N(CH_3)_2$ subject to the proviso that at least one of is R_4 and R_5 is $-NO_2$, or a pharmaceutically acceptable salt or salt hydrate of such a compound to reduction to give a compound having formula (IV) wherein R_4 and R_5 are as defined above subject to the proviso that at least one of is R_4 and R_5 is $-NH_2$, or a pharmaceutically acceptable salt or salt hydrate of such a compound;

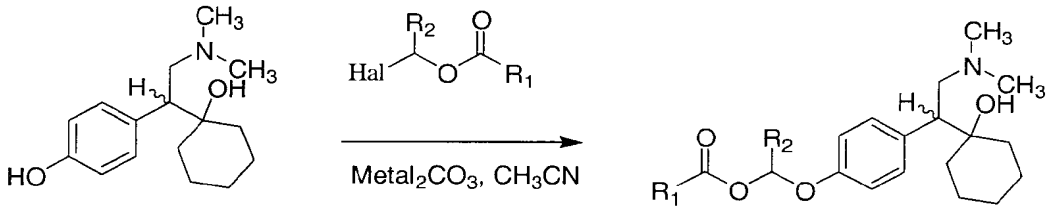
or

(iii) separating a compound having formula (I) wherein R_1 and R_2 are as defined under formula (I) in the form of an enantiomeric mixture so as to isolate a particular enantiomeric form;

or

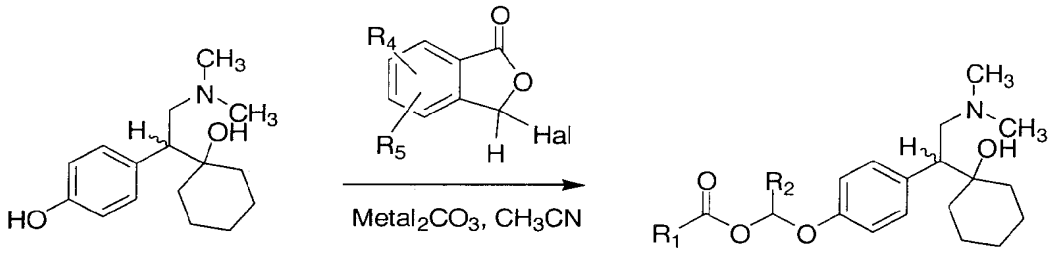
(iv) converting a compound having formula (I) wherein R_1 and R_2 are as defined under formula (I) into a pharmaceutically acceptable salt or salt hydrate thereof by addition of an acid.

With regard to process (i) above the appropriate R-, S-, or (R/S)- 4-[2-(Dimethylamino-1-(1-hydroxy-cyclohexyl)ethyl]phenol is reacted with the appropriate O-α-acyloxyalkyl halide (examples: pivaloyloxymethyl chloride, 3-bromophthalide, iodomethyl pivalate) (Scheme Ia) or (acyloxy)benzyl α-halide (Scheme Ib) in an inert solvent (acetonitrile, tetrahydrofuran, dimethylformamide) in the presence of an alkali metal carbonate (sodium or potassium carbonate) or transition metal carbonate (silver carbonate) in accordance with Schemes Ia and Ib.



ODV **I**

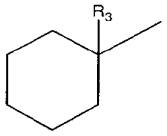
Scheme Ia



ODV **I**

Scheme Ib

wherein R_1 is selected from $C_1 - C_6$ alkyl, $C_1 - C_6$ alkoxy, $C_3 - C_6$ cycloalkyl, or the moiety:



(a);

R_2 is selected from H, or $C_1 - C_6$ alkyl;

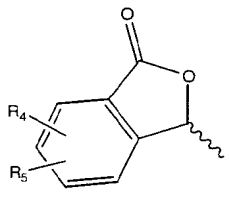
or R^2 and R^3 are concatenated to form a moiety having formula (b);

R_3 is selected from H or $C_1 - C_6$ alkyl; and

R_4 and R_5 are independently selected from H, $C_1 - C_6$ alkyl, $C_3 - C_6$ cycloalkyl, $C_1 - C_6$ alkoxy, $C_1 - C_6$ thioalkoxy, -CN, -OH, $-CF_3$, $-OCF_3$, halogen, -

NH_2, $-NO_2$, or mono or dialkylamino wherein each alkyl group has 1 to 6 carbon atoms.

In some preferred embodiments of the invention increased yield may be obtained by reacting the appropriate R-, S-, or (R/S)- 4-[2-(Dimethylamino-1-(1-hydroxycyclohexyl)ethyl]phenol with the appropriate O-α-acyloxyalkyliodide in an inert solvent (acetonitrile, tetrahydrofuran, dimethylformamide) in the presence of alkali metal carbonate such as potassium carbonate, or transition metal carbonate such as silver carbonate. Most preferred is the use of O-α-acyloxyalkyliodide in the presence of silver carbonate at low temperatures in the range of approximately 0-5° C.

In a minor modification, compounds of formula I wherein R_1 and R_2 are concatenated to form 

, and one or both of R_4 and R_5 are NH_2, can be obtained by catalytic reductions, such as with palladium catalysts, from corresponding analogs wherein R_4 or R_5 are NO_2.

Racemic 1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol can be produced as described in Example 26 of U.S. Patent No. 4,535,186 (Husbands et al.), which is incorporated herein by reference. It will be understood that the enantiomers may be separated from each other by standard resolution techniques known in the art.

Alternatively, these R and S enantiomers may be obtained by O-demethylation of the separated enantiomers of venlafaxine using either boron tribromide or ethane thiol anion.

O-α-acyloxyalkyl ethers of Formula I and their pharmaceutically useful salts and hydrates are useful for the biological and pharmacological activities for which venlafaxine and its salts are known in the art. These O-α-acyloxyalkyl

ethers may be used in treating or inhibiting central nervous system disorders, including depression, (including but not limited to major depressive disorder, biopolar disorder, and dysthymia), fibromyalgia, anxiety, panic disorder, agorophobia, post-traumatic stress disorder, premenstrual dysphoric disorder (also known as pre-menstrual syndrome), attention deficit disorder (with and without hyperactivity), obsessive compulsive disorder (including trichotillomania), social anxiety disorder, generalized anxiety disorder, autism, schizophrenia, obesity, anorexia nervosa, bulimia nervosa, Gilles de la Tourette Syndrome, vasomotor flushing, cocaine and alcohol addiction, sexual dysfunction (including premature ejaculation), borderline personality disorder, chronic fatigue syndrome, urinary incontinence, pain (including but not limited to migraine, chronic back pain, phantom limb pain, central pain, neuropathic pain such as diabetic neuropathy and postherpetic neuropathy), Raynaud's syndrome, and others. These compounds are also useful in the inducement of cognition enhancement and in regimens for cessation of smoking or other tobacco uses.

This invention also includes methods of treating, preventing, inhibiting or alleviating each of the maladies listed above in a mammal, preferably in a human, the methods comprising providing a pharmaceutically effective amount of a compound of this invention to the mammal in need thereof.

"Providing" as used herein with respect to providing a compound or substance covered by the invention, means either directly administering such a compound or substance, or administering a prodrug, derivative or analog which forms an equivalent amount of the compound or substance within the body.

A pharmaceutically effective dose will include those doses which provide the relief or prevention sought for the malady in question. The compounds of this invention may be provided in the dosages and pharmaceutical formulations known in the art as useful for venlafaxine hydrochloride (such as those doses known for the venlafaxine hydrochloride products marketed by Wyeth-Ayerst Laboratories under the Effexor® trademark). It will be understood that the initial dose, increases therefrom and final daily administration will be determined by a medical professional considering the needs and conditions for each recipient. For instance, a daily dose for

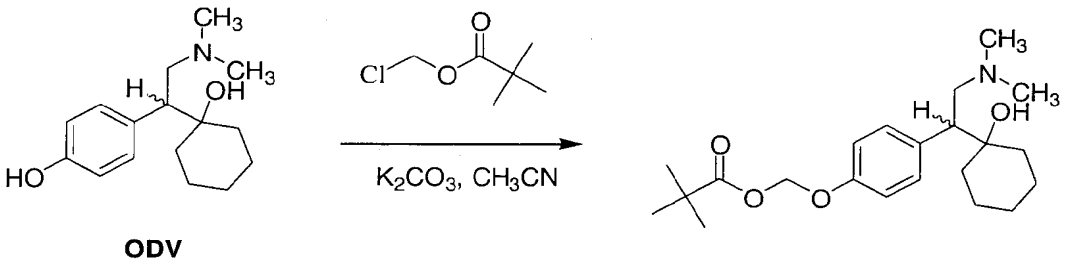
an adult human may be from about 75 mg to about 450 mg per day, preferably between about 75 and about 225 mg per day. An initial dose of 75 mg per day may be administered, with increases as determined by a medical professional.

This invention also includes pharmaceutical compositions comprising a pharmaceutically effective amount of a compound of this invention and one or more pharmaceutically acceptable carriers or excipients. A preferred method of administration includes the use of the present compounds in extended release formulations of the type described in published PCT application WO 99/22724 (Sherman et al.), which is incorporated herein by reference.

The present invention is exemplified, but not limited by, the following specific examples.

Example 1

{4-[2-(Dimethylamino)-1-(1-hydroxy cyclohexyl)ethyl]phenoxy} methyl pivalate.



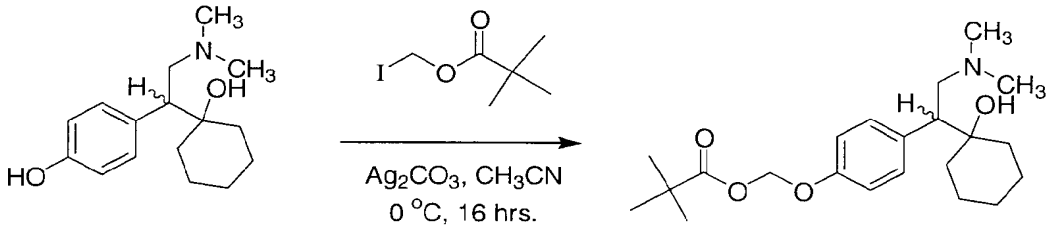
ODV

4-[2-(Dimethylamino)-1-(1-hydroxycyclohexyl) ethyl]phenol (1g, 3.79mmol), chloromethyl pivalate (0.75g, 5mmol), anhydrous K_2CO_3 (0.7 g, 5 mmol) and KI (75mg, 0 .5 mmol) were stirred in acetonitrile (50mL) and refluxed overnight. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The ethyl acetate was dried ($MgSO_4$) and evaporated to give the title compound as a minor component. IR (KBr) 1758cm^{-1}.

MS(+)FAB[M+H]$^+$378.3 calcd. For $C_{22}H_{35}NO_4$ 377.

Example 2

{4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy}methyl pivalate



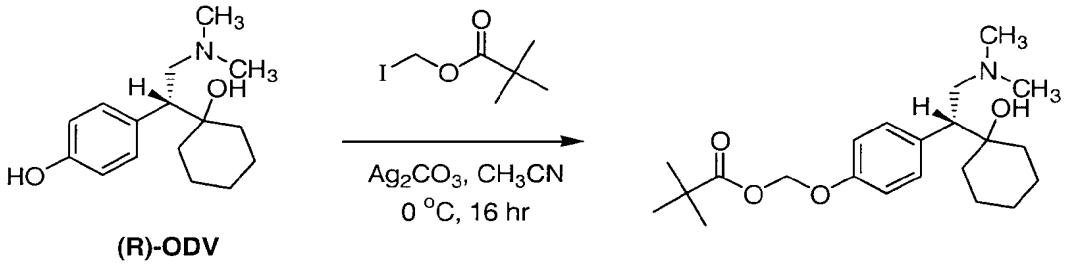
ODV

To a solution of ODV (2.0 g, 7.6 mmol) and silver carbonate (8.4 g, 30.4 mmol) in acetonitrile (60 mL) at 0 °C was added a solution of iodomethyl pivalate (prepared as described by Bodor, et al., *J. Org. Chem.* 1983, 48, 5280-5284.) (3.4 g, 14.0 mmol) in acetonitrile (100 mL) dropwise over 4 hr. The reaction mixture was filtered through diatomaceous earth (CELITE, Celite Corporation, Lompoc, CA), then absorbed onto a activated magnesium silicate (60-100 mesh) (FLORISIL, U.S. Silica Company). and purified by column chromatography (FLORISIL, ethyl acetate: acetonitrile 9:1) to afford the title compound (0.87 g, 45 %, based on 68 % conversion) as a yellow tinted semi-solid: ^{1}H NMR (CD_3CN) δ 0.78-1.0 (m, 2H), 1.19 (s, 9H), 1.15-1.35 (m, 4H), 1.4-1.7 (m, 4H), 2.2 (s, 6H), 2.25 (dd, J = 11.2, 4.5 Hz, 1H), 2.94 (dd, J = 11.2, 4.5 Hz, 1H), 3.22 (t, *J* = 11.2 Hz, 1H), 5.7 (s, 2H), 6.95 (d, *J* = 8.7 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H); ^{13}C-NMR (CD_3CN) δ 22.22, 22.44, 26.91, 27.10 (t), 32.83, 38.78 (t), 39.55 (s), 45.71 (q), 52.58, 61.74, 74.45 (d), 86.78 (t), 116.54, 131.48 (d), 136.68, 156.44, 178.05 (s); MS (ESI) *m/z* 378 $(M+H)^+$; further characterized as the maleate salt. Anal. ($C_{26}H_{39}NO_8$-0.25H_2O) Calc: C: 62.69, H: 7.99, N: 2.81, Found: C: 62.68, H: 7.68, N: 2.65.

The celite cake was taken up in brine and extracted with ethyl acetate. Evaporation of the solvent affords 0.65 g (33%) recovered ODV.

Example 3

4-[(1R)-2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenyl pivalate

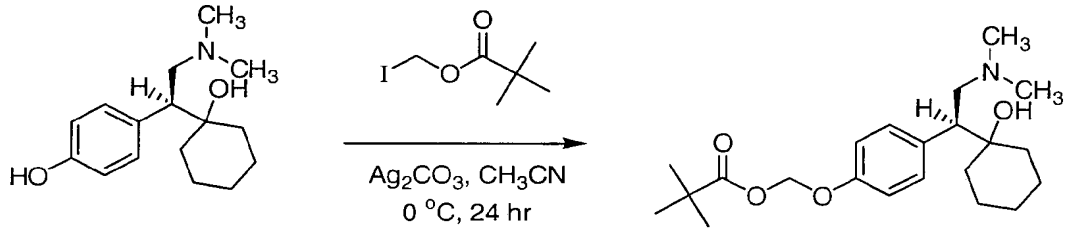


To a solution of ODV (3.0 g, 11.4 mmol) and silver carbonate (12.6 g, 45.6 mmol) in acetonitrile (300 mL) at 0 °C was added a solution of iodomethyl pivalate (prepared as described by Bodor, et al., *J. Org. Chem.* 1983, 48, 5280-5284.) (6.9 g, 28.5 mmol) in acetonitrile (40 mL) in eight equal portions over 16 hr. The reaction mixture was filtered through diatomaceous earth (CELITE, Celite Corporation, Lompoc, CA), then absorbed onto activated magnesium silicate (60-100 mesh) (FLORISIL, U.S. Silica Company) and purified by column chromatography (FLORISIL, ethyl acetate: acetonitrile 9:1) to afford the title compound (1.15 g, 39 %, based on 60 % conversion) as a white foam: ^{1}H NMR (CD_3CN) δ 0.78-1.0 (m, 2H), 1.19 (s, 9H), 1.15-1.35 (m, 4H), 1.4-1.7 (m, 4H), 2.2 (s, 6H), 2.25 (dd, J = 11.2, 4.5 Hz, 1H), 2.94 (dd, J = 11.2, 4.5 Hz, 1H), 3.22 (t, *J* = 11.2 Hz, 1H), 5.7 (s, 2H), 6.95 (d, *J* = 8.7 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H); ^{13}C-NMR (CD_3CN) δ 22.22, 22.44, 26.91, 27.10 (t), 32.83, 38.78 (t), 39.55 (s), 45.71 (q), 52.58, 61.74, 74.45 (d), 86.78 (t), 116.54, 131.48 (d), 136.68, 156.44, 178.05 (s); $[\alpha]^{20}_D$ -5.95° (*c* 1.00, MeOH); MS (ESI) *m/z* 378 (M+H)+.

The CELITE cake was taken up in brine and extracted with ethyl acetate. Evaporation of the solvent affords 1.2 g (40%) recovered ODV.

Example 4

4-[(1S)-2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenyl pivalate



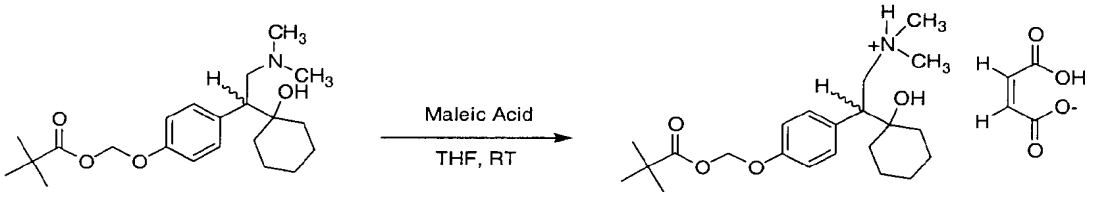
(S)-ODV

To a solution of ODV (4.0 g, 15.2 mmol) and silver carbonate (16.8 g, 60.8 mmol) in acetonitrile (400 mL) at 0 °C was added a solution of iodomethyl pivalate (prepared as described by Bodor, et al., *J. Org. Chem.* 1983, 48, 5280-5284.) (8.3 g, 34.3 mmol) in acetonitrile (150 mL) over a 9 hr period. The reaction mixture was filtered through diatomaceous earth (CELITE, Celite Corporation, Lompoc, CA), then absorbed onto activated magnesium silicate (60-100 mesh) (FLORISIL, U.S. Silica Company). and purified by column chromatography (FLORISIL, ethyl acetate: acetonitrile 9:1) to afford the title compound (1.58 g, 48 %, based on 57 % conversion) as a clear viscous oil: ^{1}H NMR (CD_3CN) δ 0.78-1.0 (m, 2H), 1.19 (s, 9H), 1.15-1.35 (m, 4H), 1.4-1.7 (m, 4H), 2.2 (s, 6H), 2.25 (dd, J = 11.2, 4.5 Hz, 1H), 2.94 (dd, J = 11.2, 4.5 Hz, 1H), 3.22 (t, *J* = 11.2 Hz, 1H), 5.7 (s, 2H), 6.95 (d, *J* = 8.7 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H); ^{13}C-NMR (CD_3CN) δ 22.22, 22.44, 26.91, 27.10 (t), 32.83, 38.78 (t), 39.55 (s), 45.71 (q), 52.58, 61.74, 74.45 (d), 86.78 (t), 116.54, 131.48 (d), 136.68, 156.44, 178.05 (s); $[\alpha]^{20}_{D}$ +7.23° (*c* 1.00, MeOH); MS (ESI) *m/z* 378 (M+H)+.

The CELITE cake was taken up in brine and extracted with ethyl acetate. Evaporation of the solvent affords 1.7 g (43%) recovered ODV.

Example 5

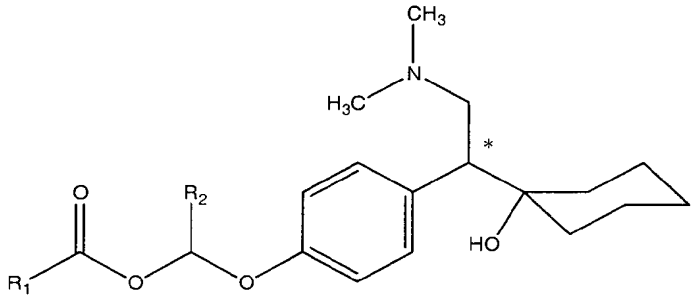
{4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy}methyl pivalate Maleate salt



To a solution of {4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy}-methyl pivalate (0.032 g, 0.085 mmol) prepared as described in Example 1, in THF (1.0 mL) at RT was added a solution of maleic acid (0.007 g, 0.06 mmol) in THF (1.0 mL). The mixture was warmed and diluted with hexane. The solution was cooled and the resulting crystals filtered off giving the desired maleate salt as a white solid: mp 112-113 °C, ^{1}H NMR (DMSO-d_6) δ 0.9-1.6 (m, 10H), 1.13 (s, 9H), 2.7 (br.s, 6H), 2.97 (m, 1H), 3.55 (m, 2H), 4.59 (br.s, 1H), 5.78 (s, 2H), 6.02 (s, 2H), 7.03 (d, J = 8.6 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 8.4 (br.s, 1H); MS (ESI) m/z 378 (M+H)+; ($C_{26}H_{39}NO_8$-0.25H_2O) Calc: C: 62.69, H: 7.99, N: 2.81, Found: C: 62.68, H: 7.68, N: 2.65.

CLAIMS:

1. A compound of the Formula (I):

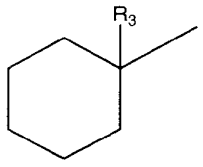


(I)

wherein

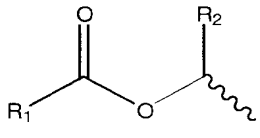
the configuration at the steriogenic center (*) may be R, S, or RS (the racemate);

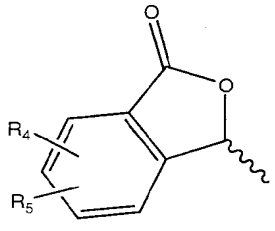
R_1 is selected from $C_1 - C_6$ alkyl, $C_1 - C_6$ alkoxy, $C_3 - C_6$ cycloalkyl, or the moiety:



(a);

R_2 is selected from H, or $C_1 - C_6$ alkyl; or,

R_1 and R_2 may be concatenated such that  , form a moiety having formula (b):



(b);

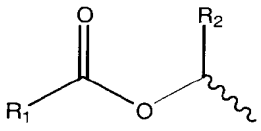
R_3 is selected from H or $C_1 - C_6$ alkyl; and

R_4 and R_5 are independently selected from H, $C_1 - C_6$ alkyl, $C_3 - C_6$ cycloalkyl, $C_1 - C_6$ alkoxy, $C_1 - C_6$ thioalkoxy, -CN, -OH, $-CF_3$, $-OCF_3$, halogen, $-NH_2$, $-NO_2$, or mono or dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, or a pharmaceutically acceptable salt or hydrate thereof.

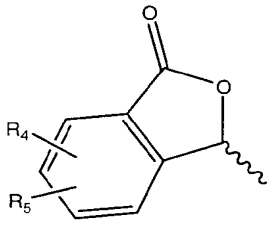
2. A compound of Claim 1 wherein R_1 is $C_1 - C_6$ alkyl or $C_1 - C_6$ alkoxy.

3. A compound of Claim 1 or Claim 2 wherein R_2 is $C_1 - C_6$ alkyl.

4. A compound of Claim 1 wherein R_1 and R_2 are concatenated such that



, form a moiety having formula (b):



(b)

and R_4 and R_5 are hydrogen.

5. A compound of Claim 1 which is {4-[2-(Dimethylamino)-1-(1-hydroxy cyclohexyl)ethyl]phenoxy} methyl pivalate, or a pharmaceutically acceptable salt or hydrate thereof.

6. A compound of Claim 1 which is 1-{4-[2-(dimethylamino)-1-(1-hydroxy-cyclohexyl)ethyl]phenoxy}ethyl propionate, or a pharmaceutically acceptable salt or hydrate thereof.

7. A compound of Claim 1 which is 3-{4-[2-(dimethylamino)-1-(1-hydroxy-cyclohexyl)ethyl]phenoxy}-2-benzofuran-1(3H)-one, or a pharmaceutically acceptable salt or hydrate thereof.

8. A pharmaceutical composition comprising a compound of Formula I as claimed in any one of claims 1 to 7, or a pharmaceutically acceptable salt or hydrate thereof; and a pharmaceutically acceptable carrier or excipient.

9. A method of treating disorders of the central nervous system in a mammal, the method comprising providing to a mammal in need thereof a pharmaceutically effective amount of a compound of Formula I as claimed in any one of claims 1 to 7, or a pharmaceutically acceptable salt or hydrate thereof.

10. The method of Claim 9 wherein the central nervous system disorder is selected from one or more of the following:
depression; generalized anxiety disorder; panic disorder; post traumatic stress disorder; attention deficit disorder, with and without hyperactivity; anxiety; schizophrenia; cocaine addiction; alcohol addiction; premenstrual dysphoric disorder and autism.

11. The method of Claim 9 wherein the central nervous system disorder is anorexia nervosa, bulimia nervosa, vasomotor flushing, and chronic fatigue syndrome.

12. The method of Claim 9 wherein the central nervous system disorder is urinary incontinence.

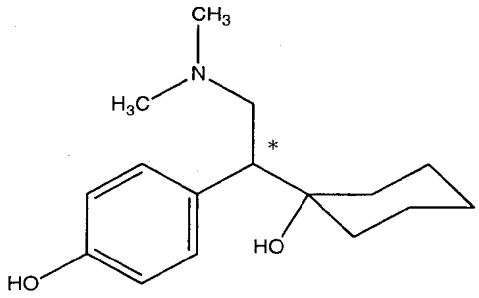
13. The method of Claim 9 wherein the central nervous system disorder is pain.

14. The method of Claim 9 wherein the central nervous system disorder is sexual dysfunction.

15. A method of enhancing cognition in a mammal, the method comprising providing to a mammal in need thereof a pharmaceutically effective amount of a compound of Formula I as claimed in any one of claims 1 to 7, or a pharmaceutically acceptable salt or hydrate thereof.

16. A process for the preparation of a compound having the formula I as claimed in claim 1, or a pharmaceutically acceptable salt or hydrate thereof, which process comprises one of the following:

(i) reacting R-, S-, or (R/S)- 4-[2-(dimethylamino-1-(1-hydroxycyclohexyl)-ethyl]-phenol of formula:



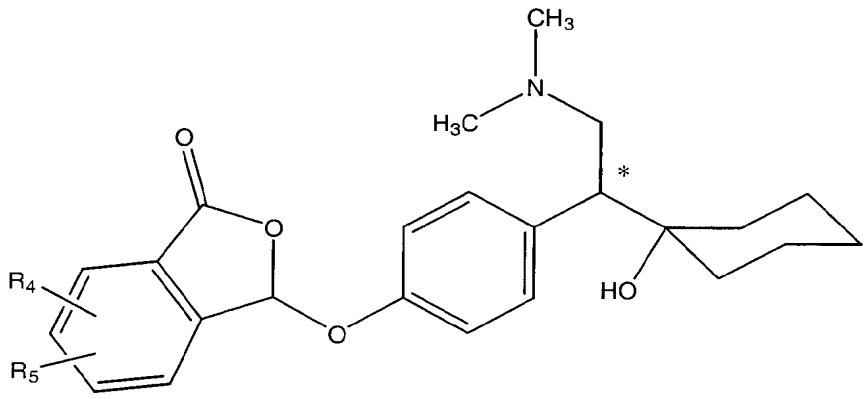
(II)

with a compound having the formula (V)

$$R_1 - CO - CHR_2 - X \qquad (V)$$

where R_1 and R_2 are as defined above subject to the proviso that an -OH or $-NH_2$ substituent on the concatenated R_1 and R_2 group may be protected by a protecting group that is subsequently removed and X is a leaving group; or

(ii) reducing a compound having formula (IV)



(IV)

wherein the configuration at the stereogenic center (*) may be R, S, or RS (the racemate) and R_4 and R_5 are independently selected from H, $C_1 - C_6$ alkyl, $C_1 - C_6$ alkoxy, $C_1 - C_6$ thioalkoxy, -CN, -OH, $-CF_3$, $-OCF_3$, halogen, $-NH_2$, $-NO_2$, or $-N(CH_3)_2$ subject to the proviso that at least one of is R_4 and R_5 is $-NO_2$, or a pharmaceutically acceptable salt or salt hydrate of such a compound, to give a compound having formula (IV) wherein R_4 and R_5 are as defined above, with the proviso that at least one of is R_4 and R_5 is $-NH_2$, or a pharmaceutically acceptable salt or salt hydrate of such a compound;

or

(iii) separating a compound having formula (I) wherein R_1 and R_2 are as defined under formula (I) in the form of an enantiomeric mixture so as to isolate a particular enantiomeric form;

or

(iv) converting a compound having formula (I) wherein R_1 and R_2 are as defined under formula (I) into a pharmaceutically acceptable salt or salt hydrate thereof by addition of an acid.

INTERNATIONAL SEARCH REPORT

PCT/US 00/31895

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C217/74 C07C213/06 A61K31/135 A61P25/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	YARDLEY J P ET AL: "2-PHENYL-2-(1-HYDROXYCYCLOALKYL)ETHYLAMIN E DERIVATIVES: SYNTHESIS AND ANTIDEPRESSANT ACTIVITY" JOURNAL OF MEDICINAL CHEMISTRY,AMERICAN CHEMICAL SOCIETY. WASHINGTON,US, vol. 33, 1990, pages 2899-2905, XP000891765 ISSN: 0022-2623 cited in the application table 1 -----	1-16

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 March 2001	13/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	O'Sullivan, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

PCT/US 00/31895

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.